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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,550	01/25/2002	Brett P. Monia	ISPH-0625	5088

7590 07/16/2003

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,550	MONIA, BRETT P.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 6-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed April 25, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed January 29, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim 1 stand rejected under 35 U.S.C. 102(b) as being anticipated by Carroll et al., for the same reasons of record as cited in the Office action mailed January 29, 2003.

Applicants traversed the rejection above on the ground that the claim as amended is now directed to the target of SEQ ID NO: 64 which is human, and that the reference of Carroll et al. discloses only a single antisense compound targeted to codons 1-6 of murine, not human c-raf. As such, applicants argue that Carroll et al. does not teach all the elements of applicants claim, which is directed to human c-raf of SEQ ID NO: 64.

This is not considered convincing, because a sequence alignment of the antisense oligo of Carroll et al. reveals that it is a perfect complement of the instant human target of SEQ ID NO: 64. Please see attached sequence alignment. Because Carroll et al. teach an antisense sequence that inhibits the murine homologue of the instant human c-raf target of SEQ ID NO: 64, and

because said antisense sequence is also perfectly complementary to applicants instant target, said antisense sequence is also considered to have the inherent function of inhibiting the instant target of SEQ ID NO: 64, absent evidence to the contrary.

Claim Rejections - 35 USC § 103

Claims 1, and 6-12 are rejected, under 35 U.S.C. 103(a) as being unpatentable over Carroll et al. in view of Bonner et al., (Nucleic Acids Res. 14 (2), 1009-1015 (1986), newly cited), Cook (WO 93/13121) and Skorski et al. (J. Clin. Inv. 1993, 92:194-202).

This rejection is similar to that of record, but has been amended to address the limitation of applicants amendment which now recites the target of SEQ ID NO: 64, and to include claim 12, also amended. Applicants' arguments as they pertain to this new rejection are addressed after the body of the rejection.

The invention of the above claim is drawn to an oligonucleotide 8 to 50 nucleotides in length that hybridizes with and inhibits c-raf expression of SEQ ID NO: 64, or modifications of said oligonucleotides comprising the incorporation of phosphorothioate linkages, or 2' sugar substitutions, or wherein said oligonucleotides comprise pharmaceutical compositions that may contain chemotherapeutic agents, and to methods of use thereof.

Carroll et al. teach an antisense sequence 18 nucleotides long that specifically hybridizes with c-raf (Raf-1 of Carroll et al.) and inhibits its expression. Although it is not known if the target of Carroll is SEQ ID NO: 64 as instantly claimed, the oligo of Carroll has 100% complementarity to the instant target of SEQ ID NO: 64 as described above, and since Carroll

teaches that said oligo has inhibitory activity, is therefore considered to inhibit said target. Carroll et al. also teach that c-raf is required for erythropoietin-mediated cellular proliferation. Carroll et al. do not teach antisense sequences comprising phosphorothioate backbone or 2'-sugar modifications, or compositions comprising said compounds and pharmaceutically acceptable diluents or chemotherapeutic mixtures thereof.

Bonner et al. teach the cDNA sequence of SEQ ID NO: 64, applicants' instantly claimed target.

Cook et al. teach modifications of oligonucleotides that comprise 2' fluoro substitutions, and the incorporation of phosphorothioate linkages, wherein said oligonucleotides may be comprise pharmaceutical compositions.

Skorski et al teach oligonucleotides comprising a pharmaceutically acceptable carrier in combination with a chemotherapeutic agent.

It would have been obvious to one of ordinary skill in the art to make oligos directed to SEQ ID NO: 64, since the sequence was taught by Bonner et al., and since Carroll et al. expressly teach antisense inhibition of c-raf. It also would have been obvious to incorporate the 2' sugar and phosphorothioate modifications of Cook into the antisense sequence of Carroll et al. or those antisense sequences made from the cDNA sequence of Bonner. Further, it would have been obvious to one of ordinary skill in the art to combine the antisense oligonucleotide of Carroll et al. with chemotherapeutic agents as taught by Skorski et al.

One would of ordinary skill would have been motivated to make and use the instant antisense compounds on human cells, because c-raf is known to be involved in cellular proliferation, a process that underlies the development of cancer, and because such antisense

compounds have been expressly taught by Carroll et al. to inhibit c-raf in mouse cell cultures. One would have been motivated to modify said antisense compounds as taught by Cook, because Cook teaches that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation. One would also have been motivated to combine the antisense compound of Carroll et al. with chemotherapeutic compounds as taught by Skorski et al., because Skorski et al. teaches that such combinations have additive effects in treating cancer cells. One would have a reasonable expectation of success in creating such modified antisense compounds because both Cook and Skorski et al. teach the steps and provides examples of how to make such compounds, and because such steps are routinely performed by those of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Regarding Applicants arguments, Applicants' state that, when viewed alone, none of Carroll et al., Cook et al., or Skorski et al. teach or suggest antisense compounds targeted to the specific regions of the c-raf transcript of SEQ ID NO: 64 as presently claimed. This argument is not adopted. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is acknowledged that the references when viewed individually do not teach the presently claimed invention; however, the test for obviousness is what the *combined* teaching of the prior art would have suggested to those of ordinary skill in the art. As indicated above, one of ordinary skill in the art would have been

motivated to make antisense oligonucleotides on human cells, because c-raf is known to be involved in cellular proliferation, a process that underlies the development of cancer, and because such antisense compounds have been expressly taught by Carroll et al. to inhibit c-raf in mouse cell cultures. Therefore, one would have been motivated to make other inhibitors, such as the instantly contemplated antisense molecules. Moreover, because Cook et al., or Skorski et al et al. teach that synthesizing and using antisense oligos to inhibit transcripts of known sequence is routine to one of ordinary skill in the art, this combination also provides a reasonable expectation of success which render the invention of the claims above obvious under 35 U.S.C. § 103(a).

Claim Rejections - 35 USC § 112

Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for antisense oligos of Isis 5136 targeted to the c-raf transcript in the treatment of pancreatic, renal cell, colon or bladder cancer. The specification as filed does not provide guidance on the *in vivo* inhibition of SEQ ID NO: 64 in treating any and all forms of cancer, or ocular angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of c-raf in human cells or tissues comprising contacting said cells or tissues with antisense compositions that inhibit the expression of c-raf. The claims of the above invention are also drawn to methods of

treating an animal having a condition associated with c-raf, wherein said compositions are administered to animals such that expression of c-raf is inhibited, wherein said condition may be a hyperproliferative disorder including cancer, or ocular angiogenesis. The language of said claims encompasses both *in vivo* treatment. The specification teaches a method of using the claimed compositions to inhibit the expression of c-raf *in vitro* and in mouse xenografts *in vivo*, or in humans in the treatment of pancreatic, renal cell, colon or bladder cancer using Isis 5136.

The specification as filed does not provide any guidance or examples beyond those sequences with exemplified *in vivo* activity that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of any antisense compound *in vivo* is problematic. Thus, even though Isis 5136 has been exemplified by applicants in the treatment of specific cancer types, the specification only provides prophetic guidance in regards to the use of any antisense compound in the treatment of cancer. Although applicants specfication discloses general methodologies of using the broad class of claimed constructs *in vivo* in methods of treatment, such a disclosure would not be considered enabling for such a broad genus, since the state of antisense-mediated gene inhibition is unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate that predicting the success of antisense-mediated treatments *in vivo* from tests that do not mimic or re-create *in vivo* conditions is problematic.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application does not provide adequate guidance for one of skill in the art to overcome the obstacles of predicting the success of specific sequences *in vivo* without ever having tested them in an *in vivo* analogous model system, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of c-raf expression *in vitro* as being correlative or representative of the successful *in vivo* use of any antisense compound in the broad treatment methods directed to any and/or all conditions or diseases suspected of being associated with c-raf expression. The specification as filed fails to provide a nexus between the problems cited and treatment achieved, beyond the sequence of Isis 5131 in the treatment of certain cancers in humans.

Said claims are drawn very broadly to methods of treating cells *in vivo* or to treating or preventing any condition or disease suspected of being associated with c-raf expression in humans, or any cancer, using any oligo directed to applicants instant target of SEQ ID NO: 64. Since the specification fails to provide any guidance for the successful treatment or prevention of such a broad range of diseases beyond the disclosed successful use of Isis 5131, and since resolution of the various complications in regards to targeting a particular gene in an organism is

highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation in order to find any other sequences with the claimed treatment efficacy. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. Beyond that guidance from the specification that describes the use of Isis 5131 in the treatment of the specific cancers disclosed, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz
July 10, 2003

Karen Lacourciere
KAREN LACOURCIERE
PATENT EXAMINER